R E M A R K S

Claims 245, 247-255, 262, 265, 268-271 are pending in the above-referenced application.

1. The Rejection Under 35 USC §112 (Enablement)

Claims 245, 247-255, 262, 265, 270, and 271 has been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Office Action specifically states in the last two paragraphs of page 7:

> It is noted that introns can be inserted into genes to control the expression of the gene, as evidenced by the state of the art; (including Gatermann; and Yoshimatsu and Nagawa et al., as cited by applicant). However, none of the references are enabling for a broad method of inserting any intron into any position of any sequence encoding any gene product wherein the resultant eukaryotic sequence would express more than one copy of a sequence. None of these references enable the instant genus of predictable splicing of any intron inserted at any position with a sequence encoding any polymerase or gene product.
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> Again, the issue is not whether it was known in the art how to insert introns, but rather how to insert introns in a predictable fashion in accordance with the breadth of the instant claims and have the desired outcome specific to eukaryotic and prokaryotic cells with regards to any polymerase, as recited in the instant claims. Balvay et al. is simply an example that secondary structure is one complexity when considering splicing mechanisms. The instant claims embrace insertion into locations such as those taught by Balvay.

In response, it is Applicants view that it was known in the art how to insert introns in a predictable fashion. The sequences of numerous introns were widely published at the time of the priority date of the instant application. Further, as noted in previous response, one of ordinary skill in the art would certainly not be constrained to selecting a sequence blindly with only the final experimental

results available to determine whether an appropriate choice of an intron has been made. As such, even prior to doing a single experiment in a laboratory, the skilled artisan would be able to select and evaluate an intron and evaluate the sequence to determine the presence of stop codons as well as predict effects on frame shifts after an insertion event.

The instant specification combined with knowledge of one skilled in the art as of the priority date of the instant invention would provide sufficient guidance that would enable a skilled artisan to make the disclosed nucleic acid constructs contain sequences that are spliced out by cellular machinery. In particular, as noted above, Example 19 provides a more than adequate teaching of a construct containing a polymerase (and toxic gene) and eukaryotic (non-native) intron and source of these sequences. This example provides a more than sufficient description regarding strategies used in choosing intron sequences to be used, insertion sites in the T7 polymerase gene and vectors. Construction steps are exemplified in Figures 26-33. This in Applicants view would provide a sufficient roadmap to one of skilled in the art for obtaining the claimed constructs.

In contrast to the position stated in the Office Action, there is ample evidence that insertion of a selected intron cassette into a particular site should generate a predictable spliced product (see, for example, Schwartz et al. 1993, Mayeda et al. 1990, Gatermann et al., 1989, Mol. Cell Biol. 9:1526-1535). It is well established case law that 100% certainty is not required and that it is sufficient that it be predictable enough to be able to avoid an undue amount of experimentation. This is certainly the case with respect to the claimed construct.

With respect to Balvay et al., there is no evidence in this reference that directly contradicts Applicants' position and the authors themselves acknowledge a lack of working examples that tested their concepts. Balvay does not contain a single word with regard to predicting results that would take place when an intron is inserted into a new exon location and is only concerned with native RNAs that exhibit aberrant splicing patterns. Their tentative conclusions are based on a speculation of the authors trying to explain why the normal expected patterns that would normally be predicted did not take place with these exceptional cases. In

Applicants view, a proper reading of Balvay is that predictable patterns of splicing are the norm but aberrant examples of splicing following abnormal patterns is likely due to secondary structure considerations.

In view of the above arguments, Applicants assert that the rejections under 35 USC §112, First paragraph (lack of enablement) has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

2. Double Patenting

Claims 245,247-255,262,265,270, and 271 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of co-pending Application No. 11/929,055. Applicants note that this is a provisional rejection. Applicants will address this rejection upon indication of allowable subject matter.

3. The Rejection Under 35 USC §102

Claim 255 and 265 have been rejected under 35 USC §102(b) as being anticipated by Schwartz et al. The Office Action specifically states:

> Schwartz et al. teaches introduction of an intron from a hamster gene into a neo gene such that splicing o the neo gene mRNA results in the synthesis of active aminoglycoside phosphotransferase. The unspliced construct is inactive in E. coli, but confers resistance to G418 when transfected into mouse and hamster cells. Schwartz et al. is evidence that it was known in the art to utilize the insertion of introns to control expression of a gene product in prokaryotic versus eukaryotic cells.

Applicants respectfully traverse the rejection. It is well established case law that anticipation requires that the claimed invention to have been known in the prior art "in the detail of the claim" such that each element and limitation contained in the claim is present in a single prior art reference, "arranged as in the claim". *Karsten Mfg. Corp. v. Cleveland Golf CO.* 242 F.3d 1376, 58 USPQ2d 1286 (Fed. Cir. 2001). This is not the case here. In Schwartz, the gene expressed an altered protein in which additional amino acids were present due to the

presence of flanking exon sequences associated with the inserted intron when introduced into a cell capable of mRNA processing. As stated on page 4 of the specification,

> .....when introduced into a cell capable of mRNA processing, the gene expressed an altered protein in which additional amino acids were present due to the presence of flanking exon sequences associated with the inserted intron. This limitation is inherent in this approach since this method of intron isolation requires the a priori presence of inherent restriction sites in the exon regions flanking the intron, and intron insertion requires the presence of appropriate restriction sites in the gene receiving the intron. Therefore, even after the excision of the intron from the RNA, the flanking exon sequences remain as part of the coding sequence of the mature RNA molecules. Furthermore, the number of sites for intron insertion on the receiving gene is severely limited by the availability of appropriate restriction sites.

Claims 255 and 262 would not be anticipated by Schwartz. Claim 255 recites that the gene product would be toxic specifically to a prokaryotic cell in the absence of the intron. This would not be the case in Schwartz, since this reference discloses insertion of intron sequences into the neo gene. Expression of the neo gene in a prokaryotic cell would not be toxic to bacteria. It is even noted in Schwartz that bacteria containing the intron were unable to grow on agar plates containing G418, whereas those not containing the intron were able to grow on such agar plates. Further, claim 255 recites that the intron sequence is within the sequence encoding the gene product. In Schwartz, an altered gene product is expressed, one containing extra amino acids.

Claim 262 would also not be anticipated by Schwartz. Claim 262 recites that the intron sequence is inserted within a sequence encoding the gene product and is immediately 3' to (C/A)AG. In Schwartz, the intron sequence is actually inserted after the additional Pro Ala Asp Phe Pro Asn Leu amino acid sequence, not within the neo gene. Further, there is no mention regarding (C/A) AG.

6. The Rejection Under 35 USC §103

Claims 245, 247-255, 262, 265, 270, and 271 have been rejected under 35 USC §103(a) as being unpatentable over Schwartz et al. in view of Mount and Deuschle et al. The Office Action specifically states:

> Schwartz et al. teaches introduction of an intron from a hamster gene into a neo gene such that splicing of the neo gene mRNA results in the synthesis of active aminoglycoside phosphotransferase. The unspliced construct is inactive in E. coli, but confers resistance to G418 when transfectd into mouse and hamster cells. Schwart et al. is evidence that it was known in the art to utilize the insertion of introns to control expression of a gene product in prokaryotic versus euaryotic cells.
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> Schwartz et al. do not teach the system specific to a polymerase, do not teach (C/A)AG sites.
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> Mount teaches splice junction sequences such as (C/A)AG and teach that the sequences have a possible role as signals for processing.
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> Deuschel et al. teach the development of a highly regulated expression system in mammalian cells in which transcription of a foreign gene is mediated by the bacteriophage T3 RNA polymerase under the control of the E. coli lac repressor. Deuschel et al. teach that a specific transcription activity can be regulated over a range of several orders of magnitude in higher eukaryotic cells…..
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> ….It would have been obvious to insert the intron into a sequence encoding a polymerase given that it was known in the art that bacteriophage T3 RNA polymerases are crucial in gene expression systems that regulate genes in eukaryotic cells. One would have been motivated to do so in order to attempt to control the expression of the polymerase in prokaryotic/eukaryotic cells since Schwartz et al. teaches that introns can be inserted to control differential expression.

Applicants respectfully traverse the rejection. As noted above, Schwartz actually teaches that the gene expressed is an altered protein in which additional amino acids are present due to the presence of flanking exon sequences associated with the inserted intron. Therefore, even after the excision of the

intron from the RNA, the flanking exon sequences remain as part of the coding sequence of the mature RNA molecules. The alteration of the gene product by the Schwartz approach may have unpredictable effects on the function of the gene product and severely limits the applicability of this method to specific instances. In the example of Schwartz et al., the additional amino acids had no apparent effect on the activity of the protein synthesized in the capable cell, but this is not always a predictable quality since it depends upon the site where the additional amino acids are incorporated. Therefore, it would be questionable as to whether there would be sufficient motivation to combine the cited references. Furthermore, at best the combination of Schwartz, Mount and Deuschel would result in a polymerase + extra amino acids + intron sequence, not the subject matter recited in claims 245, 247-255, 262, 265, 270, and 271.

In view of the above arguments, Applicants assert that rejection of claims 245, 247-255, 262, 265, 270 and 271 under 35 USC 103 have been overcome. Therefore, Applicants respectfully request that these rejections be withdrawn.

7. Conclusion

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

/Cheryl H Agris/

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